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Research Article

Low Dose Risperidone Every 3.8 Hours: Superior Efficacy in Treatment of Bipolar Disorders

Robert W Townsend*

Department of Clinical Mental Health, Private Mental Health Clinic, 4273 Montgomery Blvd NE, Suite 240-East, Albuquerque, United States

ABSTRACT

Background: This paper presents a previously unpublished Bipolar Disorder treatment using low-dose Risperidone that gives superior-efficacy, prevents overmedication, and prevents medication-induced anxiety and irritability. Standardized other Bipolar Disorder treatments have a failure rate of 82% to 87.1%. When dropouts and poor adherence are combined, only 12.9% to 18% of bipolar patients adhere to medications within three years. Self-defensive providers primarily blame bipolar patients for treatment failures. When that bias is removed, failure is due to overmedication and anxiety and irritability caused by medications. This paper shows the neurobiochemical processes that cause those problems. Published prescription-guidelines recommend Risperidone in high amounts that intentionally activate its 9-Hydroxyrisperidone metabolite under auspices that it is virtually the same as Risperidone and lasts for 24 hours. In truth, however, the beneficial Risperidone chemical lasts for four hours and 9-Hydroxyrisperidone agonizes Bipolar-toxic Serotonin. Low-dose Risperidone neutralizes 9-Hydroxyrisperidone.

Methods: Low doses of Risperidone were calculated to be therapeutic amounts without causing overmedication, anxiety, and irritability. Doses were calculated to metabolize low plasma concentrations of 9-Hydroxyrisperidone that stay below the neural-activation threshold level. Four-hour-duration low doses of Risperidone were administered every 3.8 hours.

Results: 3.8-hour dosing sustained steady benefits by overlapping 15-minute efficacy-onset with the 15-minute termination of each previous dose. Steady transitions between doses and five administrations per day gave therapeutic efficacy for 16 hours. Taking dose #5 at bedtime gave improved sleep.

Conclusion: Low doses of Risperidone activate its therapeutic benefits while neutralizing Bipolar-toxic Paliperidone. Low-dose Risperidone every 3.8 hours maintains stability with room for adding occasional extra doses to control exacerbations of symptoms. This study provides a new biochemistry-based Bipolar Disorder treatment that is vitally needed because the failure rate of traditional treatments is too high. Traditional treatments and research are guided by commercial drug manufacturers' recommendations and data. Traditional treatment dropout and non-adherence rates attest to the immediate need for this paper's new paradigm of analytic neurobiochemistry.

Keywords: 9-Hydroxyrisperidone; 9-OH-Risp; Efficacy-duration; Invega; Paliperidone; Risp; Risperdal; Risperidone

Abbreviations: AA: Arachidonic Acid; FDA: Food and Drug Administration; hr: hour; J&J: Johnson and Johnson; kg: kilogram; lb: Pound; MD: Medical Doctor; mg: Milligram; min: Minute; P: Paliperidone; R: Risperidone; µg/L: Micrograms per liter.

INTRODUCTION

This paper presents a groundbreaking and vastly superior new paradigm for treating Bipolar Disorders. This author is unaware of any other studies of the neurobiochemistry processes and Bipolar Disorder treatment methods presented in this paper. Risperidone is used in the Mental Health profession as a major mood stabilizer and as an antipsychotic. Risperidone has two main components: (1) A chemical with the scientific name Risperidone and (2) 9-Hydroxyrisperidone, an antipsychotic-metabolite of Risperidone also known as Paliperidone. Risperidone was FDA

Correspondence to: Robert W. Townsend, Department of Clinical Mental Health, Private Mental Health Clinic, 4273 Montgomery Blvd NE, Suite 240-East, Albuquerque, United States, E-mail: RtWTown@cs.com

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approved for Bipolar Disorder treatment in 1993 under the brand name Risperdal. Paliperidone is not FDA-approved for Bipolar Disorder treatment. The FDA rejected Paliperidone-Invega for Bipolar treatment in 2006, 2009, and 2011. This is the first paper known to this author to analyze the Bipolar-toxic properties of Paliperidone. This is the first paper known to this author to present a vastly superior method of Bipolar Disorder treatment that uses low-dose Risperidone every 3.8 hours and neutralizes Bipolar-toxic Paliperidone.

51.5 million Adults in the United States (20.6%) reportedly experienced Mental Health problems during 2019. Forty-six million people worldwide reportedly had Bipolar Disorders during 2018 with a reported 2.8% prevalence of Bipolar Disorders in the USA during 2019. Common Bipolar Disorder treatments combine antiepileptics such as Valproic Acid and antipsychotics such as Risperidone. Risperidone is a 4-hour chemical that metabolizes into 24-hour Paliperidone. This is the first research paper to strictly differentiate between Risperidone, Paliperidone, and an ostensive active moiety. Standard daily Risperidone of 2 mg to 8 mg or more metabolizes activation-amounts of Paliperidone. Little known laboratory studies show Paliperidone increases Prolactin and Serotonin. Standard-dose Risperidone exceeds effective small amounts by 400% to 1600%, causing unnecessary Risperidone overmedication for four hours followed by 21 hours of harmful Serotonin agonism by Paliperidone.

To the best knowledge of this author this is the first research paper to address those issues. To the best knowledge of this author this is the first research paper to overcome those issues by developing a superior new Bipolar-treatment with low-dose Risperidone every 3.8 hours. Low doses of 0.25 mg, 0.5 mg, 0.75 mg, and 1.0 mg activate the benefits of Risperidone without activating Paliperidone. Administration every 3.8 hours sustains efficacy by overlapping 15-20-minute efficacy-termination of one dose and 15-20-minute onset of the next dose. This new method is overtly superior to the universally accepted 30-year standard. Neurobiochemistry data in this paper is from a review of scientific literature. Case study information is from the author's outpatient treatment experiences with Bipolar Disorder patients. Drug-manufacturer information is from a review of history literature.

Definitions of technical terms

Activation: Minimum serum concentration that initiates/triggers synaptic responses.

Threshold: Below the threshold, a medication is biochemically inert or inactive. At or above the threshold, a medication is biochemically active or activated. This is strictly biochemical. It does not imply noticeable, clinical, or primary effects.)

Active moiety: A manufacturer-promoted widely accepted false concept in Risperidone product inserts that says Risperidone and Paliperidone are a single entity. The misleading marketing gimmick claims (a) 4-hour-duration Risperidone has the 24-hour duration of Paliperidone and (b) 24-hour lesser-efficacy-Paliperidone has the greater-efficacy of 4-hour Risperidone.

Manufacturer: Johnson & Johnson (J&J) invented, owns rights, produces, and markets Risperdal/Risperidone and Invega/Paliperidone. Product labels and other product literature are often printed and published under the name Janssen Laboratories or Janssen, a J&J subsidiary owned and controlled by J&J. Other manufacturers also produce and sell generic Risperidone and Paliperidone.

Paliperidone: Chemical name 9-Hydroxyrisperidone was first discovered as a chemical metabolite of Risperidone. Paliperidone has been isolated and is manufactured separately by J&J as an Antipsychotic medication under the brand name Invega. The Risperdal product insert says the half-life of Paliperidone is 21 hours. The Invega insert says 23 hours.

Risperdal: "Risperdal" has two definitions: (a) J&J and Janssen's brand name for Risperidone. (b) An active moiety combination of Risperidone-efficacy and Paliperidone-efficacy.

Risperidone chemical name: Risperidone is the scientific name of a specific chemical compound. The reported half-life varies across studies from 2.8 to 3.4 hours. Efficacy and biochemical duration are generally agreed to be 4 hours. In this paper the names Risperidone, chemical-Risperidone, and chem-Risperidone are used for the specific Risperidone chemical compound as differentiated from (a) the metabolization process, (b) metabolites such as Paliperidone, (c) Risperdal (see definition above), and (d) an ostensive active moiety combination of Risperidone and Paliperidone.

METHODOLOGY

Aim of this study

This paper is an independent Humanitarian work that brings the world a critically needed paradigm of scientific neurobiochemistry to safely and effectively help people who have a Bipolar Disorder.

Design of this study

This paper is based on data found online in approximately 120 existing documents (Description of Materials Used in This Study below).

Setting of this study

This author owns and operates a one-person private practice Mental Health clinic that is not used for experimental research. This author's research consists of extensively gathering and analyzing information documents and research studies found on the internet.

Characteristics of study participants

Four of this author's Bipolar Disorder clinical patients and two of their household family members signed consent forms allowing medication-pertinent treatment information to be mentioned in this paper. These were not experiment subjects. They did not actively participate in this study.

Description of materials used in this study

Internet searches gathered a wide range of scientific research documents, prescription guidelines, drug product package inserts,

letters and other documents exchanged back and forth between the FDA and the manufacturer, FDA documents evaluating the manufacturer's Approval Application research reports, clinical efficacy research studies, laboratory in-vivo investigations of chemical properties and interactions.

Description of the processes used in this study

Four of this author's Bipolar Disorder clinical patients and two of their household family members signed consent forms allowing medication-pertinent treatment information to be mentioned in this paper. These were not experiment subjects. They did not actively participate in this study.

Interventions used in this study

No experimental interventions were used in this study.

Comparisons used in this study

Risperidone was compared to Paliperidone vis á vis review and analysis of data in existing documents found online regarding dose-related clinical efficacy, duration of clinical efficacy, chemical structure, duration of chemical structure, neurobiochemical properties, neurobiochemical actions and potentials, histories of product development, and histories of FDA approvals

Type of statistical analysis used in this study

Basic Algebra was used for calculating Risperidone dose-amounts, plasma concentrations, and activation thresholds.

Risperidone reduces dopamine and serotonin

Bipolar Disorders have a neurobiochemical trait of receptor-synapses that absorb excessive amounts of Dopamine and Serotonin. This over-activates the nervous system, e.g., the brain. Medications that reduce synaptic-absorption of Serotonin and Dopamine can calm and stabilize bipolar nerves and brains. Reductions can occur through antagonism of receptors, antagonism of natural production of Dopamine and Serotonin, antagonism of transporter-cell bonding and production, and increased reuptake. Low serum concentrations of Risperidone can reduce synaptic absorption of Dopamine and Serotonin. Increased serum concentrations can further decrease absorption of Dopamine and Serotonin.

Two definitions of "Risperidone"

The word "Risperidone" has two definitions: 1) in scientific chemistry "Risperidone" is the scientific name, or chemical name¬, of a specific 4-hour duration chemical. Its unique chemical-identification number (CID) is 5073. Its unique chemical structure is C23H27FN4O2. In scientific chemistry it is distinctly differentiated from its metabolite chemicals. 2) In commercial drug marketing "Risperidone" is the generic name of the brand name medication "Risperdal" that is marketed as an inextricable combination (active-moiety) of the name-ingredient and its 23-to-26-hour duration metabolite Paliperidone (9-Hydroxyrisperidone). This paper avoids confusion by using "chemical-Risperidone" as a topic or paragraph lead-in for the scientific chemistry definition [1].

Onset-time, half-life and efficacy-duration

Chemical-Risperidone has a short half-life of 2.8 to 3.5-hours depending on which source is being cited [1-4]. A study with 19 pediatric inpatients [2] showed a half-life of 3.0 hours. The study showed Risperidone plasma levels dropped to dose-administration levels (horizontal red line in Figure 1, below) at 4 hours then dropped below dose-administration levels. Adult patients at this author's Mental Health clinic consistently reported the effects of Risperidone fade noticeably between 3.9 and 4 hours and end at about 4 hours. Patients' reports were consistent with household members' reports, this author's clinical observations, and the above study. The plasma concentration drops below the dose-administration level and efficacy ends at about 4 hours. This author's patients also consistently reported that beneficial effects of Risperidone are noticeable 15 to 20 minutes after ingestion. This was also consistently reported by patients' house hold members and was consistently observed by this author hundreds of times (Figure 1).

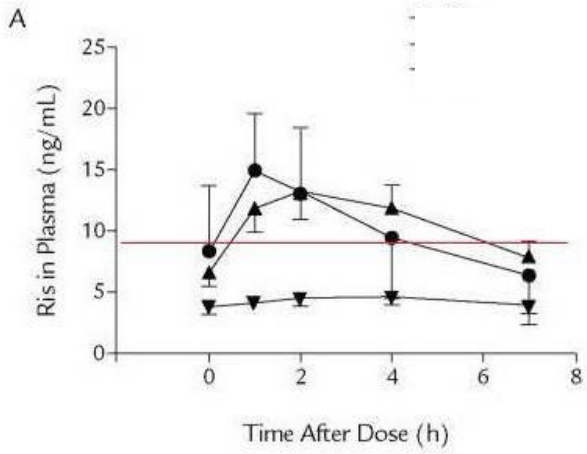

Figure 1: Chemical-Risperidone and Paliperidone plasma durations. **Note:** (●) Ris; (▲) (+)-9-OH-Ris; (▼) (-)-9-OH-Ris.

Efficacy duration is independent of dose-amount, length of use, and adjunctive medications

Participants in the above study were 19 pediatric inpatients ages 4 to 16 of several diagnostic categories. All were on established maintenance Risperidone therapy twice per day prior to and during the study. Doses ranged from 0.25 mg BID to 2.5 mg BID. Four participants were on Risperidone monotherapy. Fifteen participants were taking concurrent medications with a wide range of amounts wherein some took 10 times more than others. Among the participants the half-life and duration of Risperidone were constant regardless of dose-amount, length of use, type and amount of co-medication, diagnosis, age, and gender. Research studies consistently show that among the vast majority of people Risperidone metabolizes completely into other chemicals at or very near the 4-hour mark.

15-20-minute onset-time, moot half-life and 4-hour duration

Onset: Several research studies report a median T-max of 1-hour and a dose dependent C-max [3]. This is the first paper this author knows of that includes patient-reported efficacy onset time of chemical-Risperidone. This author's Bipolar Disorder treatment patients and their participating household members consistently reported an onset-time of 15 to 20 minutes after pill ingestion. The author also consistently observed the 15 to 20 minute onset-time during clinical therapy sessions. The short onset time is an important component of the Bipolar Disorder treatment method presented in this paper.

Half-life: The traditional definition of "half-life" states that after five half-lives a chemical is 94% eliminated and after six half-lives it is 98% eliminated. The half-life of Risperidone is reportedly 2.8 hours, 3 hours, 3.2 hours, or 3.4 hours (the mean among these reports is 3.1 hours) depending on which source is cited [4-8]. On one hand, given the reported the shortness of the half-life, a 36-minute difference among reports is considerable. One the other hand, this is the first research paper that the author knows of to show that the traditional concept of "half-life" is moot for Risperidone. The median reported half-life is 3.1 hours, whereby it would be 98% eliminated only after 18.6 hours. However, what actually happens is this:

a) On one hand, a 3.1-hour "half-life" is too long. Four hours after intake the chemical structure of Risperidone metabolizes into several other chemicals whereby the chemical structure of Risperidone becomes disassembled and no longer exists. Risperidone has 4 hour duration, not a 3.1-hour "half-life".

b) On the other hand, a 3.1-hour "half-life" is too short. The manufacturer has cleverly convinced everyone (other than this author) that Risperidone is combined with a metabolite with a half-life of 20 to 25 hours. Everyone (except this author) dogmatically believes "Risperidone and Paliperidone" are 98% eliminated at 120 to 180 hours although everyone also believes Risperidone has a 3.1-hour half-life.

The reports of a 2.8 to 3.4 hour half-life and a 20 to 25 hour half-life are not valid predictors of Risperidone elimination. The short-half-life reports and the long-half-life reports misrepresent the 4 hour coherence and efficacy of Risperidone. The traditional definition of "half-life" is irrelevant for Risperidone. The applicable time-measure for Risperidone is duration.

Duration: Chemical-Risperidone duration regards the starting point and ending point of three interrelated factors: 1) specific chemical-structure, 2) chemical-specific neural responses, and 3) chemical-specific clinical efficacy. C-max and T-max occur at 1-hour. Plasma concentration then decreases for three hours to the initial intake level. When an intake level is above zero due to a previous dose, the level drops below intake to zero about 10 minutes after hour-4 [8]. All of the author's Bipolar Disorder patients reported that noticeable effects begin 15-20 minutes after dose-intake and effects start fading about five minutes before they end at about hour-4 (Figure 2).

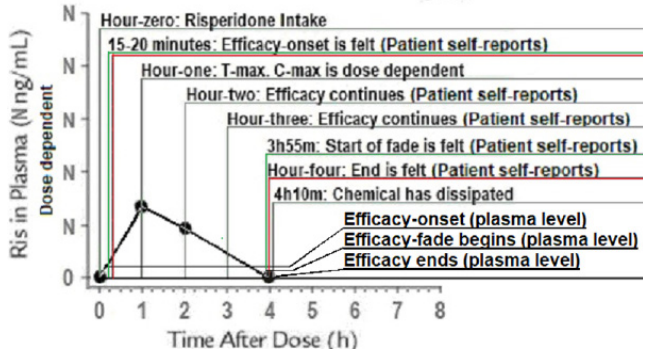

Figure 2: Patient-reported efficacy onset and duration, and plasma concentration duration. **Note:** (–●–) Ris.

Superior responses from a lower blood level

Oral tablet Risperidone is more clinically potent than Paliperidone. This is partially due to bioavailability of 68% versus 28% respectively. The difference in bio availabilities is largely due to a higher Paliperidone affinity for efflux protein Pgp (ABCB1). This affinity decreases brain exposure to medications by reducing brain tissue permeability [9]. A significantly higher percent of blood-borne Risperidone passes through the blood-brain barrier tissues to enter the brain. The brain-absorption of higher quantities of Risperidone enables lesser amounts of medication to induce superior efficacy. The good bioavailability of Risperidone might be advantageous for any diagnostic category of patients who use antipsychotics. It is particularly advantageous for patients with Bipolar Disorders. Bipolar Disorders cause Dopamine and Serotonin to over-activate the brain and the nervous system. Effective antipsychotics calm the brain and nerves by reducing Dopamine and Serotonin absorption. Reduction is done by receptor inhibition, transporter-cell inhibition, and inhibition of production.

Risperidone is a benzisoxazole derivative. It is a selective monoaminergic antagonist with a high affinity for binding to and occupying Serotonin and Dopamine synaptic receptors. It has a ten to twenty time's higher affinity for 5-HT2A receptors than for D2 receptors [8]. It significantly decreases both Dopamine and Serotonin absorption. It also inhibits absorption in other ways. A laboratory investigation of Risperidone vs. Paliperidone neural-activation functions and neural-responses spoke of "concentrations of paliperidone (3 μM) and risperidone (1 μM)" that were "obtained from concentration-response curves for signaling responses at 5-HT2A and 5-HT2C receptors." The investigation found that three times less Risperidone than Paliperidone induced neural responses [6].

In the laboratory investigation serum concentrations for neural responses had a 1-to-3 ratio of Risperidone-to-Paliperidone. Neural responses to Paliperidone differed from responses to Risperidone. 1 μM of Risperidone significantly reduced the release and functions of Serotonin transporter Arachidonic-acid (AA). A three times higher amount of 3 μM Paliperidone

increased AA sensitivity causing AA transporter cells to gather increased amounts of Serotonin and carry it to receptors. Researchers found that the differing effects on AA significantly impacted the amounts of Serotonin that were absorbed by 5-HT2A and 5-HT2C receptors. Risperidone reduced the number of AA transporters and decreased the amount of Serotonin that transporter cells brought to synaptic receptors. By allowing less incoming Serotonin the amount of Serotonin that was absorbed by receptors decreased. Paliperidone made AA transporters more efficient. By not reducing their number an increased amount of Serotonin was brought to synaptic receptors. Thereby the amount of Serotonin that was absorbed by synaptic receptors increased (Figures 3 and 4).

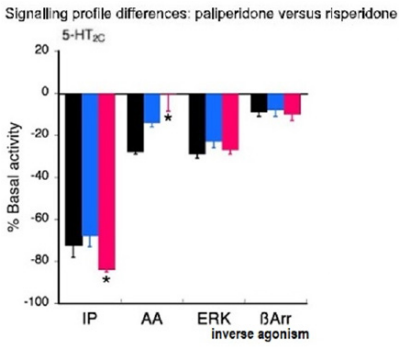

Figure 3: Binding-affinity of serotonin transporter-cells. **Note:** (■) SB206553; (■) Risperidone; (■) Palliperidone.

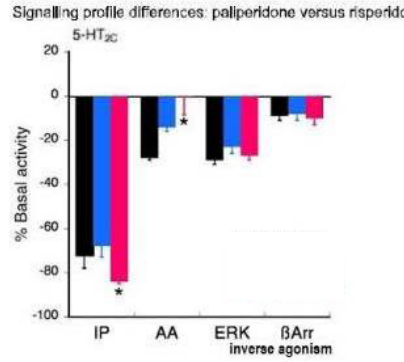

Figure 4: Production/release of serotonin transporter-cells. **Note:** (■) SB206553; (■) Risperidone; (■) Palliperidone.

Odou, et al. found that in a response in 5-HT2C receptors, Risperidone was an inverse agonist and reduced basal AA release by 14 ± 2%. By contrast, Paliperidone reduced basal AA release by only 0.5 ± 8% and behaved as an agonist. In 5-HT2A receptors only Risperidone significantly reduced AA release (17 ± 4%). Another comparative study found Risperidone occupied 17% more D2-Dopamine receptors and 28.2% more 5-HT2A-Serotonin receptors. The reported D2-receptor affinity of Paliperidone was three times lower than that of Risperidone. Risperidone occupied a greater number of D2 and 5-HT2A receptors. The occupied receptors were less able to absorb Dopamine and Serotonin [10]. Activation of neural response requires three times higher serum concentrations of Paliperidone and the resulting Paliperidone responses are harmful to Bipolar Disorders.

Differential-activation: Activating Risperidone while neutralizing Paliperidone

The neuropsychiatric benefits of Risperidone can be activated without neural responses to Paliperidone. To the best knowledge of this author this is the first research paper regarding differential-activation of Risperidone and Paliperidone. This is the first research paper to show differential-activation is possible. This research paper also is the first to present a treatment method that activates the benefits of Risperidone without activating responses to Paliperidone. This topic is new and critically important for the treatment for Bipolar Disorders.

Many people in the Medical and Research Communities are aware that Serotonin destabilizes Bipolar Disorders and that Risperidone is a Serotonin antagonist. The vast majority of Medical and Research people are unaware that metabolite Paliperidone is a Serotonin agonist that needs to be neutralized for safe and effective treatment of Bipolar Disorders. Key factors for accomplishing this critically necessary differential-activation include:

A. At about 4-hours Risperidone metabolizes into other chemicals including Paliperidone.

B. Risperidone efficacy occurs at low serum concentrations that metabolize inactive small amounts of Paliperidone [6].

C. Risperidone metabolizes into 77.35% of its volume in Paliperidone, yielding 22.65% less Paliperidone than Risperidone [9].

D. The activation-threshold serum concentration of Paliperidone is three times higher than activation-threshold of Risperidone [6].

To the best awareness of this author, this is the first paper to show that it is beneficial to activate the psychoactive properties of chemical-Risperidone while not activating the psychoactive properties of Paliperidone. To the best awareness of this author, this is the first paper to show that it is possible to activate to activate the psychoactive properties of chemical-Risperidone while not activating the psychoactive properties of Paliperidone. To the best awareness of this author, this is the first paper to show how to activate the psychoactive properties of chemical-Risperidone while not activating the psychoactive properties of Paliperidone. When providing clinical treatment for Bipolar Disorders it is critical to differentially activate the former and not the latter. Chemical-Risperidone is a powerful Serotonin and Dopamine antagonist [11]. Paliperidone is a harmful Serotonin agonist and a weak Dopamine antagonist. Key factors for calculating a differential-activation regimen include:

1. Efficacy of Risperidone occurs at low serum concentrations.

2. At about 4-hours Risperidone metabolizes into other chemicals.

3. The metabolites are inert other than Paliperidone.

4. The serum concentration activation-threshold of Paliperidone is three times higher than the serum concentration activation-threshold of Risperidone [6].

5. Risperidone metabolizes into 77.35% of its volume in Paliperidone, yielding 22.65% less Paliperidone than Risperidone [2].

An active-moiety research article by Odou et al. studied Paliperidone serum concentrations in relationship to clinical-efficacy. The authors wrote, "Statistical analysis revealed a significant increase in efficacy when the serum concentration of active drug was between 25 and 150 µg/L..." This author marked the level of clinical efficacy from Paliperidone 25 µg/L with vertical red line in Figures 5 and 6 shows "active-moiety" (Paliperidone) plasma concentration levels and corresponding Risperidone dose-amounts per day.

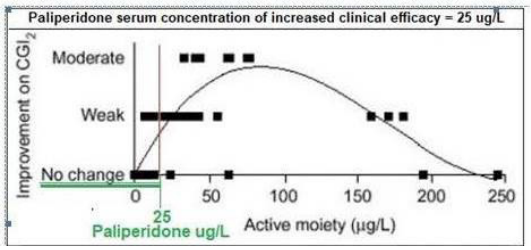

Figure 5: Paliperidone 25 ug/L triggers clinical efficacy.

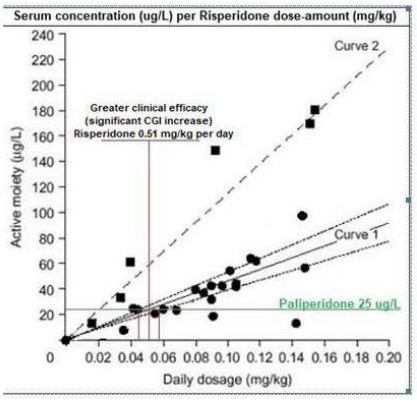

Figure 6: Daily amount of Risperidone for Paliperidone 25 ug/L.

On Figure 6 this author marked 25 µg/L with a horizontal green line that intersects the Curve-1 efficacy-mean at the 0.051 mg/kg point. This is equivalent to 4.627 mg for a 200-pound person, 3.933 mg for 170-pounds, 3.47 mg for 150-lbs, 3.0073 mg for 130-lbs, 2.6603 mg for 115-lbs, or 2.3133 mg for 100-lbs [12]. This yields Paliperidone 25 µg/L and the above-mentioned significant increase in clinical efficacy (Figures 5 and 6).

The phrase "significant increase in efficacy" said minimal efficacy occurred at a lower concentration than 25 µg/L. This author re-analyzed the data and found minimal Paliperidone efficacy occurred at 23.9 µg/L.

This corresponds with Risperidone 0.05 mg/kg, equivalent to 4.5 mg for a 200-lb person, 3.75 mg for 170 lbs, 3.5 mg for 150-lbs, 3 mg for 130-lbs, 2.5 mg for 115-lbs, or 2.25 mg for a 100-lb person (Figures 7 and 8) [12].

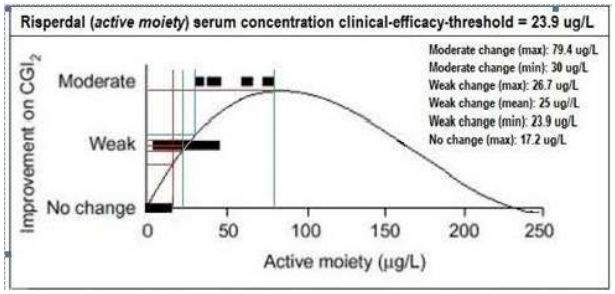

Figure 7: Clinical global impression rating and plasma concentration.

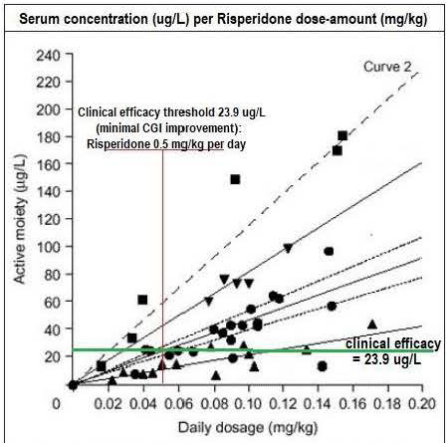

Figure 8: Amount of risperidone for paliperidone 23.9 ug/l.

The above study listed mg/kg dosages per body weight. The average weight of USA males is 197.9 pounds and 170.6 pounds for females [13-15] (Tables 1 and 2). According to data from the above study, minimum clinical efficacy of Paliperidone requires a Paliperidone serum concentration of 23.9 µg/L. That requires Risperidone daily dose-amounts of 4.48 mg for average-weight males and 3.87 mg for average-weight females [16] (Tables 3 and 4).

The calculated dose-amounts for healthier-weight and average-weight USA Americans correspond to the Paliperidone serum concentration that was associated with minimal clinical efficacy on CGI2 test-scores. The clinical efficacy dose-amounts and serum concentration seem to affirm a synaptic-activation threshold but biochemical data is needed in order to correctly identify a synaptic threshold and dosage parameters.

Table 1: Average weight of USA adult males.

How much does the average American man weigh?
The average American man 20 years old and up weighs 197.9 pounds*. The average waist circumference 40.2 inches and the average height is Just over 5 feet 9 inches (about 69.1 inches) tall.
When broken down by age group the average weights for American men are as follows:

Age group (Years)	Average weight (Pounds)
20-39	196.9
40-59	200.9
60 and older	194.7

Table 2: Average weight of USA adult females.

How much does the average American woman weigh?	
The average American woman 20 years old and up weighs 170.6 pounds*. And stands at 63.7 inches (almost 5feet 4 inches) tall.	
And the average waist circumference? Its 38.6 inches.	
As of 2016 the average weights for women in different age group were*	
Age group (Years)	Average weight (Pounds)
20-39	167.6
40-59	176.4
60 and older	166.5

Table 3: Paliperidone minimum-efficacy daily dose-amount of Risperidone for average-weight USA male.

Your weight	197.9 lb
Dosage	0.05 mg/kg
Frequency	Once per day
Total daily dose	4.488 mg

Table 4: Paliperidone minimum-efficacy daily dose-amount of Risperidone for average-weight USA females.

Your weight	170.6 lb
Dosage	0.05 mg/kg
Frequency	Once per day
Total daily dose	3.869 mg

The 4.48 mg and 3.87 mg dose-amounts were for average-weight USA Americans. Such persons are significantly overweight. Their dose-amounts may be too high for persons of healthier weight. In order to find dose-amounts for persons of healthier weight, this author used the weight-range means for average height males (5'9", 156.66 pounds) and females (5'4", 131.33 pounds). The calculated daily dose-amount for healthier-weight men is 3.55 mg and 2.98 mg for healthier-weight women (Tables 5-8) [12, 13].

Table 5: Mean weight of average-height USA males.

Ideal Body Weight Charts for Men 25-29 Years of Age			
Height in feet and inches	Small frame	Medium frame	Large frame
5'2"	128-134	131-141	138-150
5'3"	130-136	133-143	140-153
5'4"	132-138	135-145	142-156
5'5"	134-140	137-148	144-160
5'6"	136-142	139-151	146-164
5'7"	138-145	142-154	149-168
5'8"	140-148	145-157	152-172
5'9"	142-151	151-163	155-176
5'10"	144-154	151-163	158-180
5'11"	146-157	154-166	161-184
6'0"	149-160	157-170	164-188
6'1"	152-164	160-174	168-192
6'2"	155-168	165-178	172-197
6'3"	158-172	167-182	176-202
6'4"	162-176	171-187	181-207

Table 6: Paliperidone minimum-efficacy daily dose-amount of Risperidone for healthier-weight males.

Your weight	156.66 lb
Dosage	0.05 mg/kg
Frequency	Once per day
Total daily dose	3.553 mg

Table 7: Mean weight of average-height USA females.

Ideal body weight charts for women 25-29 Years of Age			
Height in feet and inches	Small frame	Medium frame	Large frame
4'10"	102-111	109-121	118-131
4'11"	103-113	111-123	120-134
5'0"	104-115	113-126	122-137
5'1"	106-118	115-129	125-140
5'2"	108-121	118-132	128-143
5'3"	111-124	121-135	131-147
5'4"	114-127	124-138	134-151
5'5"	117-130	127-141	137-155
5'6"	120-133	130-144	140-159
5'7"	123-136	133-147	143-163
5'8"	126-139	136-150	146-167
5'9"	129-142	139-153	149-170
5'10"	132-145	142-156	152-173
5'11"	135-148	145-159	155-176
6'0"	138-151	148-162	158-179

Table 8: Mean weight of average-height USA females.

Your weight	131.33 lb
Dosage	0.05 mg/kg
Frequency	Once per day
Total daily dose	2.9785 mg

Factors for calculating dose-amounts that activate Risperidone without activating Paliperidone

Factors for calculating appropriate dose-amounts include but are not limited to:

1. The appropriate Risperdal/Risperidone doses are 3.2265 times less than doses that activate Paliperidone. This is a biochemical ratio with two inherent properties:

a) The needed amount of Risperidone serum concentration is three times less than the amount of Paliperidone serum concentration that affects synaptic functions 6.

b) Risperidone metabolizes into 22.65% less Palideridone than the original amount of Risperidone. Risperidone has an onset time of 15-20 minutes, a half-life of 3.2-3.5 hours, and its clinical efficacy and chemical-structure end at 4 hours [2].

Steady efficacy requires a steady serum concentration that requires taking Risperidone every 3.8 hours. Due to the frequency, routine small doses plus small extra doses taken as needed provide steady efficacy without overmedicating the patient and without activating Paliperidone. When a patient is starting Risperidone (or any psychoactive medication), introduce it slowly in a way that minimizes and/or prevents grogginess. Keep in mind that medication-grogginess is a tiredness of the body, muddied/slow thinking, and flat or irritable emotions. Medication-grogginess is the leading cause of poor adherence and quitting treatment among Bipolar Disorder patients. The new treatment paradigm in this paper prevents medication-grogginess.

Calculating differential-activation dose-amounts

Differential-activation is defined herein as an induction of neural responses to Risperidone without an induction of neural responses to Paliperidone. Differential-activation requires maintaining Paliperidone at below the serum concentration that induces neural responses to Paliperidone. The preceding re-analyses of clinical data calculated the threshold concentration of Paliperidone and the threshold doses of Risperidone. In addition to clinical data, differential-activation incorporates laboratory findings and biochemical variables such as 1) Risperidone metabolizes into a 22.65% lesser amount of Palideridone, and 2) Neural responses to Paliperidone require a serum concentration that is three times higher (a 3/1 ratio) than the Risperidone response-threshold.

The calculated Risperidone serum concentration clinical efficacy threshold is 6.5 µg/L. This is 27.2% of the Paliperidone efficacy-threshold. Thus, differential-activation occurs when a Risperidone serum concentration is below 27.2% of the Paliperidone threshold. Dose amounts for differential-activation vary according to body weight and severity of symptoms, and the severity of Bipolar symptoms fluctuates over time. Body weight is a useful constant factor in calculating dose-amounts and it can useful for preliminary calculations of five-times-per-day low doses [14-17].

Factors for calculating dose-amounts that activate Risperidone without activating Paliperidone

The amount per dose of Risperdal/Risperidone that activates synaptic responses to Risperidone is 3.6795 times less than the Risperdal/Risperidone dose-amount that activates synaptic responses to Paliperidone. This 1.0/3.6795 ratio includes three factors:

Factor-A: The minimum serum concentration of Risperidone that initiates synaptic-responses is three times less than the minimum serum concentration of Paliperidone that initiates synaptic-responses [6].

Factor-B: Risperidone metabolizes into 22.65% less (-.2265) Palideridone serum concentration than the original amount of Risperidone serum concentration [2].

Factor-C: Accuracy requires adding +.2265 per Risperidone-unit to adjust for the -.2265 metabolization-decrease. Factor-C thereby combines Factor-A and Factor-B as: 3 × (1-unit of Risperidone + .2265 metabolization-compensation). Whereby: 3 × 1.2265 = 3.6795.

Calculating Risperidone serum concentrations that activate risperidone without activating Paliperidone

Re-analyses of data from a published study of clinical-efficacy found the lowest Paliperidone serum concentration that initiates minimal neural interaction is 23.9 µg/L [2]. Dividing 23.9 µg/L by 3.6795 (Factor-C) reveals the lowest Risperidone serum concentration that initiates minimal neural activation: Paliperidone-23.9 µg/L ÷ 3.6795=6.5 µg/L-Risperidone. The minimum efficacy-threshold of Risperidone is 6.5 µg/L. Paliperidone activation will not occur as long as Risperidone metabolizes less than 23.9 µg/L-Paliperidone. This defines the serum concentration range for Risperidone-treatment differential-activation.

Differential-activation is defined herein as the induction of neural responses to Risperidone without the induction of neural responses to Paliperidone. Differential-activation has two properties and functions: 1) Maintaining Paliperidone serum concentrations below the level that induces neural responses. 2) Simultaneously maintaining Risperidone serum concentrations at levels that sustain therapeutic neural responses to Risperidone. The desired Risperidone efficacy-threshold is 6.5 µg/L. The Bipolar-harmful Paliperidone activation-threshold is 23.9 µg/L. Risperidone dose-amounts of the range of differential-activation serum concentrations vary according to body weight and severity of symptoms. Body weight can be a useful when calculating initial dose-amounts per-day [14-17] and for calculating initial amounts-per-dose for five-times-per-day low doses. Differential-activation dosages per body weight are provided below:

Differential-activation dose-range per day per body weight: 200 lb=3.27 mg-4.5 mg, 170 lb=2.55 mg-3.75 mg, 150 lb=2.24 mg-3.5 mg, 130 lb=1.746 mg-3 mg, 115 lb=1.307 mg-2.5 mg, 100 lb=1.026 mg-2.25 mg.

Differential-activation amount per dose for five doses per day (and Pharmacy-available tablets) every 3.8-hours per body weight: 200 lb=.654 mg (.5-.75 mg tabs), 170 lb=.51 mg (.5-.75 mg tabs), 150 lb=.448 mg (.5 mg tabs), 130 lb=.348 mg (.5 mg tabs), 115 lb=.2614 mg (.25-.5 mg tabs), 100 lb=.2052 mg (.25 mg tabs). Pharmacy small-dose tablets are available in 0.25 mg, 0.50 mg, and 1.0 mg. With practice, 0.50 mg and 1.0 mg tablets can be cut in half with a pill-cutter. Active ingredients are evenly distributed in each tablet. Be careful to cut as precisely as possible so the resulting dose-amounts are divided equally.

Factors for calculating dose-frequencies that sustain Risperidone efficacy without activating Paliperidone

Risperidone dose-efficacy onset time is 15-20 minutes. Efficacy starts diminishing at about 3-hours 55-minutes. Chemical-structure and efficacy end at between 4 hours and 4-hours 10-minutes [2].

Steady efficacy through the day requires a steady serum concentration by taking Risperidone five times per day, every 3.8 hours (3-hours 50-minutes). At this frequency, routine small doses provide steady serum concentration and steady maintenance efficacy without overmedicating the patient and without activating Paliperidone. Small extra doses (i.e., one or sometimes two 0.25 mg tablets) taken as needed control unpredictable Bipolar-symptom exacerbations. When a patient is starting Risperidone (or any psychoactive medication), introducing it slowly according to individualized patient comfort/tolerance minimizes and/or prevents grogginess. Keep in mind that medication-grogginess is a tiredness of the body, muddied/slow thinking, and flat or irritable emotions. Medication-grogginess is the leading cause of poor medication-adherence and is the leading cause of quitting treatment among Bipolar Disorder patients. The new treatment paradigm in this paper has superior effectiveness and prevents medication-grogginess. It thereby improves medication-adherence and keeps patients in treatment.

RESULTS

Guidelines for titration of adjunctive valproic acid and low dose Risperidone

Adjunctive therapy with Valproic acid and Risperidone is more effective than Valproic acid monotherapy or Risperidone monotherapy. Each of these medications has a set of unique benefits that are therapeutically enhanced by the unique benefits of the other medication. One of the combined benefits is that Valproic acid increases digestive absorption of Risperidone into the blood stream, whereby lower doses of Risperidone achieve therapeutic plasma concentrations with Valproic acid adjunctive therapy. Conversely, Risperidone does not affect the plasma concentration of Valproic acid [3]. Starting therapy with just Valproic acid allows it to be titrated to its optimal efficacy without confusing its effects with effects of concurrent Risperidone titration. This eliminates the risk of cross-reaction overmedication during Valproic acid titration.

Titration of valproic acid er

a) The therapeutic blood-level of Valproic acid for Bipolar treatment is typically 85 to 125 mcg/mL [18,19].

b) Exceeding 100 mcg/mL usually does not add significant benefits and there is a greater risk of side effects.

c) Titration for Valproic acid ER: Add increments of 250 mg every two or three weeks until the patient is taking 500 mg at bedtime and 500 mg 12 hours later. Monitor for grogginess during titration.

d) If there is no grogginess (or when it no longer occurs for a week), add the next titration dose.

e) Some Bipolar patients can adequately manage their symptoms with Valproic acid monotherapy. Be vigilant for that possibility.

f) Some Bipolar patients receive temporarily adequate symptom control from taking just Valproic acid during titration and for an individual-patient-dependent period of time following full titration, one to three months for some patients.

g) If Valproic acid provides the patient with adequate symptom relief, do not add Risperidone unless/until Valproic acid adequate symptom relief wanes.

h) Some Bipolar patients benefit from immediate adjunctive therapy with both Valproic acid and Risperidone in order to bring a quick halt to self-harm or physical aggression.

i) If it is appropriate, add Risperidone to fully titrated Valproic acid ER. The Risperidone titration guidelines below were developed for the treatment method in this paper.

Titration of Risperidone

Dose amounts:

a) Start with one 0.25 mg dose at bedtime to prevent initial grogginess during awake-hours. This should improve the quality of the patient's sleep without causing grogginess upon waking. If the patient experiences grogginess upon waking, continue 0.25 mg only at bedtime until the grogginess stops. It usually stops within about five days.

b) If there is no grogginess (or when it no longer occurs) from dose-1, suggest adding a second 0.25 mg daily dose to be taken routinely at a time when the patient most often feels stressed. This should reduce the patient's stress and help prevent grogginess.

c) If there is no grogginess (or when it no longer occurs) from dose-2, suggest adding a third 0.25 mg daily dose to be taken routinely at a time when the patient most often feels stressed. This should reduce the patient's stress and help prevent grogginess.

d) If there is no grogginess (or when it no longer occurs) from dose-3, suggest adding a fourth 0.25 mg daily dose to be taken routinely at 3.8 to 4 hours before or after one of the current doses.

e) If there is no grogginess (or when it no longer occurs) from dose-4, suggest adding a fifth dose and set all doses at 3.8 to 4 hour intervals.

f) If the patient says it might be beneficial, increase one dose at a time until all doses are 0.5 mg, usually the optimal amount.

g) If you think an increase to a 0.5 mg routine would be helpful but the patient says No, invite him/her to try 0.5 mg at times of stress and let you how it feels.

h) Keep the patient supplied with a week or two of extra 0.25 mg tabs (35-70 pills) for temporary usage as-needed for controlling symptom exacerbations.

i) A routine regimen of one 0.5 mg tab every 3.8 hours (x5

per day) keeps most Bipolar-patients' nerves calm enough to noticeably reduce the frequency of significant exacerbations. When a "wave" hits a patient, taking an extra 0.25 mg tab with every other routine dose can control it. Taking an extra 0.25 mg tab with every routine dose can control a harsher "big wave". While a wave diminishes, a patient can avoid overmedication by decreasing the frequency of taking extra doses. When a wave is gone, a patient returns to the routine regimen. Patients who learn how and know they can control their waves become calmer and more reasonable in general. This leads to more secure self-esteem and better relationships with others.

j) It is valuable for a patient to set cell phone reminder-alarms to ring every 3.8 hours at medication-time.

k) It is valuable for a patient to not turn off the alarm sound until the scheduled pill is taken.

Frequencies

Figure 3 below is a dose-administration timeline for steady efficacy using low amounts of Risperidone. After ingestion there is process of stomach digestion, bloodstream distribution, initial synaptic absorption, and increasing absorption. It typically takes 15-20 minutes for the synapses to absorb a threshold amount that triggers significant responses. This results in a 15-20 minute onset time for noticeable effects. The amount of Risperidone in the bloodstream increases for 1 hour then gradually diminishes to below the synaptic threshold at about 4 hours. Efficacy ends and another dose taken at 4-hours will have a 15-minute onset time. Patients will have an uncomfortable and often very troublesome 15-20 minutes of being unmedicated every 4 hours.

The roller coaster is unnecessary and can be foregone by taking a second dose 10 minutes before the first dose loses effect. The serum concentration of a dose (Dose-1) wanes as it nears the termination of its 4-hour duration. A next dose (Dose-2) brings more concentration in a slope of increase that adds a bit to the Dose-1 waning-amount at the time when the waning would otherwise drop to an amount below the efficacy-threshold. The waning amount simultaneously adds a bit to the increasing amount at a time when the increasing amount would otherwise not yet be at the efficacy-threshold amount. The two amounts cumulatively keep the serum concentration above the efficacy-threshold. Dose-2 increases on a slope at the same pace as the decrease-slope of Dose-1. They combine to sustain serum concentration threshold equilibrium during the transition from Dose-1 to Dose-2. This occurs when Dose-2 is taken 10 minutes before Dose-1 wanes below the threshold. The diminishing efficacy of one dose is offset by the increasing efficacy of the next dose. The patient remains stable. There is no efficacy roller coaster with low doses of Risperidone every 3.8-hour.

A Risperidone 1 mg dose that corresponds with 0.01 mg/kg to 0.02 mg/kg does not meet or exceed the Paliperidone-activation threshold. A 1 mg low dose does not activate Paliperidone. It does, however, induce beneficial Risperidone responses.

An added benefit of low-dose treatment is that routine maintenance doses can be augmented with small extra doses during symptom exacerbations. This is possible because low doses metabolize 22.65% less Paliperidone than their own volume and because Paliperidone activation requires three times more serum volume than Risperidone activation requires. With low dose Risperidone, Paliperidone cannot be activated by small extra doses.

The treatment-paradigm in this paper differs from other bipolar regimens in that it relies on accurate biochemistry and also fits patient-oriented perspectives. The new paradigm precludes 1) overmedication, 2) Paliperidone-increases of Serotonin and Prolactin, 3) false claims of active moiety, and 4) thirty-years of inaccurate research based on false active moiety. This new paradigm encourages treatment and minimizes dropout rates by providing markedly superior benefits without overmedication.

This author has implemented the superior method in this paper successfully for 14 years at a private practice Mental Health clinic that he owns and operates as a sole-proprietor single-providership since 1997. Four current patients use the method in this paper. They gave written consent to include their pertinent treatment and case history information in this paper. This paper is not a Multiple-Case-Study but some pertinent patient-information is valuable. One of the patients is a male 58-year-old Medical Doctor in treatment with this author for 13 years since 2008. Another patient is a 22 year-old woman in treatment with this author for six years since 2015. Another patient is a 21 year-old woman in treatment with this author for four years since 2017. The other patient is a male 45 year-old schoolteacher in treatment with this author for seven months since early-2021.

The superior benefits of the treatment method in this paper are evidenced by this author's clinical case-observations, patient self-reports, and patient household-member reports. Patient self-reports of efficacy were positive and consistent within each patient across time. Individual patient self-reports were consistent with reports by other patients across all patients. Household members said the same things as patients and members of other households. Reports by patients and household members were consistent with this author's clinical case-observations. The information from patients and household members is reliable evidence that the method in this paper overcame the above-mentioned treatment-dropout rates and family fears of treatment.

Across all patients, household members participated in treatment at home in the similar ways. Notably: a) They could sense when a patient forgot to take medications. b) They used supportive tones and words in pointing out that medications were missed and should be taken now. c) They quickly sensed exacerbations of Bipolar-symptoms. d) They used supportive tones and words to calm the patient during exacerbations. e) They sensed when an extra "booster" tab of low dose medication was the best thing for resolving an exacerbation. f) They encouraged patients to take medications on time and attend regularly scheduled Therapy sessions. g) They supportively got the patient to page the Therapist (or page on behalf of the patient) for an emergency session when exacerbated symptoms were too severe to handle at

home. They brought the patient to the clinic when exacerbated symptoms were too severe for the patient to drive safely.

Patients reported reliable treatment information that validates the benefits of the treatment method in this paper. Some key points that validate the method are:

1) the longevity of patient-treatments,

i. Seven months

ii. Four years

iii. Six years

iv. Thirteen years

2) All of the patients consistently adhere to their medications

i. Two patients started treatment as frequently-self-harming severely dysfunctional teenagers

ii. One patient is a knowledgeable and successful MD who started treatment 13 years ago

3) The MD, the 45 year-old, and the 22 year-old previously had other medications. They reported the regimen in this paper is markedly superior

4) Patient and household member reports state appreciation for the following features:

i. The low doses provided stability without overmedication

ii. The 3.8-hour dose-frequency sustained stability during transitions between doses

iii. The x5 per day dosage sustained stability through the day

iv. Sustained stability through the day contributed to better quality sleep at night

v. Consistent medication administration made symptom exacerbations less frequent and less severe

vi. Use of extra doses as-needed enabled patient-control of symptom exacerbations

vii. Flexible patient-control is a patient-oriented approach that engendered patient self-confidence and trust toward professional care

All of the involved patients have histories of quitting two to six or more other treatments in the past all of the patients and household members reported to this author, "You are the only one who knows what he's doing with medications and you're the only one who has actually helped." That says about everything that can be said to validate the benefits and superiority of the new paradigm presented in this paper.

This paper presents a method of treating Bipolar Disorders with standard Valproic acid plus low-dose Risperidone every 3.8 hours. The purpose of this method is to optimize patients' therapeutic benefits. A part of this optimization is prevention of overmedication. Another part is differential-activation of Risperidone that neutralizes counter-therapeutic Paliperidone. Bipolar Disorder treatment using adjunctive Valporic acid and differential-activation-Risperidone yields significantly superior results of safety and efficacy.

DISCUSSION

We can't change the past but we can make a better future for 46-million bipolar sufferers and their communities worldwide. When a person with a Bipolar Disorder starts Risperidone and Valproic acid it is important to maintain patient-comfort by preventing initial overmedication and grogginess.

This can be done easily by introducing low doses and slow titration. Medication-grogginess is a tiredness of the body and slow/muddy thinking that often brings flattened or irritable emotions. Bipolar patients sense the slow grogginess more acutely than most other people because they are accustomed to hyperactive nerves and racing thoughts.

Bipolar illness runs in family bloodlines. Many Bipolar families have a staunch fear of overmedication and of "all of that mental health crap". The fear is not false or delusional. The words "zombied" and "zombified" describe a reality that besets bipolar patients more often than other people due to the sedation-factor in Bipolar medications. Bipolar families fear bad/excessive medications because the reality of bad/excessive medications induces well-justified and appropriate fear in bipolar families.

The history of Risperidone and Paliperidone

Janssen Laboratories, a subsidiary of Johnson & Johnson (J&J), developed Risperidone in response to lagging sales of Haloperidol. Risperidone combined greater effectiveness with fewer side effects. "Risperidone" is the scientific name of a chemical with post-intake structural and efficacy durations of four hours. It has a unique characteristic of metabolizing into another antipsychotic, Paliperidone.

The duration of Paliperidone is 23 to 26 hours. Risperidone was FDA approved under the brand name "Risperdal" for Schizophrenia and acute bipolar mania in 1993. Paliperidone was isolated a few years later and was FDA approved for Schizophrenia in 2006 under the brand name "Invega" [10]. The FDA refused three times (2006, 2009, and 2011) to approve Paliperidone for Bipolar Disorders. The FDA and J&J didn't say it was refused or why. However, three refusals show it was for something significant. Not being told of the FDA refusals, the Medical and Research Communities are not aware that Paliperidone is somehow dangerous. Withholding the refusal information gained huge financial profits for J&J.

In 1993 there was no prior history of an antipsychotic metabolizing into an antipsychotic with a six times longer duration. Analysts at the FDA had no precedent for comparison so they relied on J&J and Janssen. Research reports said Risperidone and Paliperidone differed by only one molecule and were essentially the same (Figures 9 and 10). The FDA had nothing to contradict this so they approved Risperidone and the research report description of it.

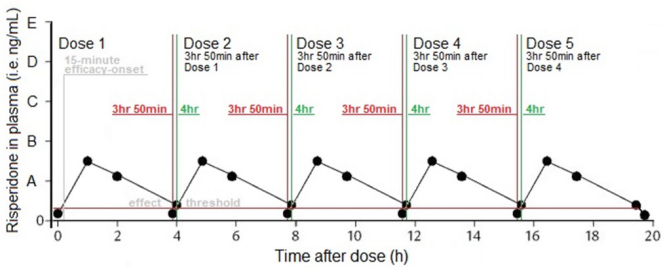

Figure 9: Risperidone 3.8-hour dosing. **Note:** (⊸) Risperidone, A,B,C,D, E: Dose-dependent plasma concentration.

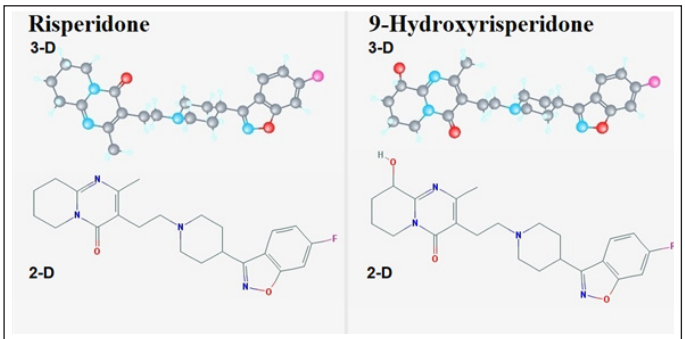

Figure 10: Diagrams of chemical-Risperidone and 9-Hydroxyrisperidone.

Misleading rhetoric in marketing and in the Risperidone FDA approval-application

Drug manufacturers' scientist-employees are legally mandated to silence and secrecy. Janssen scientists gave their Risperidone research results to the CEO of Janssen's parent company, Johnson & Johnson, around 1990. The CEO assigned the report to a Marketing Department Director who assigned it to a team of marketing experts to be rewritten. The report was finessed with linguistics and data-presentations that enhanced the likelihood of FDA-approval and maximized potential profits. Marketing Directors met with the CEO to insert more double-talk half-truths that made weaknesses seem like strengths or irrelevant outliers.

In other words, J&J linguistics experts wrote misrepresentations in the FDA Approval-Application research report. FDA approval allowed misrepresentations to be included in the "Risperdal" package-insert.

A detailed analysis of the misrepresentations is provided below: "Risperidone" was included in the word "9-Hydroxyrisperidone" and the two chemicals differed by a single molecule, so J&J rewrote the reports to say "9-hydroxyrisperidone is virtually the same as risperidone." J&J also wrote that the Pharmacokinetics of Risperidone is "similar" in "poor" and "extensive" metabolizers. They inserted that there were very few "poor metabolizers" (6%-8% are "poor metabolizers"). J&J posed an undefined "extensive" metabolizers group and an insignificantly sized "poor" metabolizers group. The word "similar" placed the two undefined groups in a single category that made them appear to be one group. The word "similar" was not defined. Therefore it was moot. But when practitioners, patients, and researchers read the product label, they will not interpret the word "similar" as moot. They will ascribe the word to something. The "poor" group and the "extensive" group were in a category as one group, so "similar" couldn't apply to them. So "similar" seemed to be a comparison of Risperidone to Palideridone.

J&J's linguistics led practitioners, patients, and researchers to interpret (assume) the label as saying: "The pharmacokinetics of Risperidone and 9-Hydroxyrisperidone are similar". In truth, the half-life of 9-Hydroxyrsiperidone is 23 to 24 hours and Risperidone is 3 hours. The efficacy of 9-Hydroxyrsiperidone is 24 to 26 hours and Risperidone has 4 hours. They are not similar. J&J's Corporate-marketing-linguistics handed the public an unsupported illusion of "similarity". The illusion deceitfully exploited the 1993 public's naïve trust in the name Johnson & Johnson. The illusion also exploited the 1992-93 FDA's naïve trust in the name Johnson & Johnson.

J&J deceptively placed 4-hour Risperidone and 24-hour Paliperidone in a single category to make them seem to be a singularity. J&J named the category "active-moiety". J&J's active-moiety marketing-linguistics made two separate chemicals (Paliperidone and Risperidone) falsely appear to be a single entity. The illusion deceitfully ascribed Paliperidone's 24-hour duration to 4-hour Risperidone. The deceptive illusion also ascribed the high-quality therapeutic-properties of Risperidone to Bipolar-toxic Paliperidone. It was marketing-linguistics genius to name the category active-moiety. The phrase has an impressive tone of advanced-level science.

The tone of advanced science placed the affair above common comprehension and enabled J&J to give active-moiety a definition filled with convoluted sophistry and tautological double talk. It was designed to seem stationed so far above common comprehension that an intelligent person wouldn't feel stupid for not understanding it. The stated definition of active-moiety was a genius masterwork of marketing-linguistics. The genius minds at Johnson & Johnson's Marketing Department outdid themselves beyond the categorically incomprehensible phrase "active-moiety" by christening the dual-entity medication with the deceptive name "Risperidone" and the brand name "Risperdal" that echoes Risperidone. Bipolar-toxic Paliperidone was linguistically consigned to oblivion although it constitutes 85% of the dual-entity medication's manufacturer-recommended efficacy duration. The misleading assigned name was not an innocent whim of happenstance. J&J knew Paliperidone was flawed.

It is best to avoid confusion in this paper by referring to the 4-hour component of the medication as "chemical-Risperidone".

J&J knew chemical-Risperidone worked well as mono and adjunct-treatment, but they decided the 4-hour medication would sell better if prescribers and the public thought it was a once-per-day 24-hour pill. J&J knew they could convince prescribers and the public of this, and even the FDA. In the world of 1990-1993 J&J knew that the name "Johnson & Johnson" was a household

word for "safety, trust, and high-quality products". The brand was squeaky-clean and All-American. It was synonymous with "No More Tears" baby shampoo and "J&J Baby Powder" [20]. J&J decided to linguistically negate the factual differences between chemical-Risperidone and Paliperidone in order to market the concept of 24-hours.

In 2020 Johnson & Johnson and Janssen were Court ordered to pay $6.8 million in legal damages and $2.2 billion in criminal penalties for damages that came from false information and false marketing of Risperidone. J&J also was Court ordered to pay $467 million for damages that came from withholding and falsifying information about J&J Baby Powder. Those lawsuits did not deal with the misrepresentations that are discussed in this paper but they show that J&J's motivation of huge financial profits makes misrepresentation a common practice.

The information above shows that Johnson & Johnson has a history of withholding and misrepresenting information about their products. That history includes withholding and misrepresenting information about chemical-Risperidone and Paliperidone. By withholding and misrepresenting information about chemical-Risperidone and Paliperidone J&J can sell 4-hour Risperidone as a 24-hour once-per-day medication. In order for Risperidone to function as a once-per-day medication it must be taken in high doses that activate the Paliperidone metabolite.

Johnson & Johnson has three financial profit motives for marketing Risperidone as a once-per-day medication:

1. Manufacturing a large quantity of low-dose pills is considerably more expensive than manufacturing the same amount of active ingredients into a small quantity of high-dose pills.

2. High dose pills sell for a considerably higher price than low dose pills.

3. Theoretically the convenience of one-pill-per-day increases patient adherence. Prescribers are more prone to prescribe a 24-hour medication than a several-times-per-day medication.

Johnson and Johnson combined the three profit factors by misrepresenting Risperidone as a one high dose per day pill. This required them to misrepresent 24-hour Paliperidone as identical to Risperidone. This required silence about the FDA not approving Paliperidone for Bipolar Disorders. This also required the withholding of information about the Bipolar-toxic properties of Paliperidone.

FDA-approval turned Risperidone into a blockbuster of global profits. Chemical-Risperidone was rewritten into a illusion of 24-hour grandeur. The Marketing Department titled the illusion "Active-Moiety".

The false construct of "Active moiety" led to overmedication, false test results, and Gynecomastia

While this author was doing Research Analysis for this paper, he inadvertently came across many surprising facts pertaining to Risperidone, Paliperidone, and the workings of the corporation that manufactures them. In addition to the topics already covered by this paper, three other topics particularly stand out as warranting discussion: 1) Dose guidelines based on active moiety resulted in chemical-Risperidone triple-amount overmedication 2) Research based on the premise of active moiety yielded false test results for Risperidone clinical efficacy and plasma concentrations. 3) Little known findings showed that Paliperidone, not chemical-Risperidone, causes significant increases in Prolactin [5]. Each of these topics warrants a full Research Analysis paper but for now they will be briefly addressed as adjuncts to this paper.

The concept of active-moiety led to overmedication

In studies that compare Risperidone to Paliperidone, the concept of active moiety keeps most research from accommodating the 4-hour efficacy of the former because it is combined with the 23-to-26-hour efficacy of the latter. In order to differentiate Risperidone variables from Paliperidone variables, test measures of the former must be administered between minute-15 and hour-3.9, ideally at hour-1 when Cmax is present. Minute-15 is the onset of noticeable-effect and effect noticeably starts to wane at 3-hr 55-min (hour-3.9) shortly before it ends at 4-hours. Valid Risperidone-results of all types are dependent on the minute-15-to-3.9-hour rule (15/3.9-rule). Valid test results of clinical efficacy depend on the 15/3.9-rule plus 1) amount(s) and frequency of Risperidone, and 2) co-medication(s), if any, that have agonist or antagonist interactions with Risperidone. Most study-subjects take Risperidone according to manufacturer-recommendations that activate Paliperidone and most take one or more co-medications.

The above factors inherently enable validity for research and serve as confounds when they are not accommodated. The 15/3.9-rule has different applications for Paliperidone variables. For example, although the product label doesn't include it, Risperidone has a half-life of 2.8-to-3.5-hours, depending on which study is cited. The Invega product label states a terminal elimination half-life of 23 hours. The Risperdal product label states Paliperidone has an apparent half-life of 21 hours, whereby 50% remains at 21 hours and 46% remains at 24 hours when the next 15/3.9-rule opportunity is present. If Risperidone-related clinical testing is done during this 15/3.9-rule opportunity, the testing will be confounded by the concomitant effects of at least 46% of the previous day's Paliperidone serum concentration.

If a subject receives the manufacturer-recommended doses of Risperidone two or three times per day, the testing will be confounded by significantly greater than 50% of the previous day's Paliperidone serum concentration. The long half-life of Paliperidone makes it impossible to test for the clinical effects of Risperidone so the manufacturer concocted the concept of active moiety to claim that the confounding interactions of Risperidone and Paliperidone are a combined strength. It is a manipulative use of language. It deflects attention from the differences between the effects of two chemicals. It also disguises the major confounds of 1) Risperidone wears off at 4 hours and leaves just the effects of Paliperidone for the next 20 hours, 84% of each 24-hours. 2) Paliperidone-activation requires 3.2265 times more serum concentration than Risperidone requires. In order meet

the requirements of Paliperidone-activation, Risperidone doses are prescribed at more than triple the Risperidone-necessary amounts.

The concept of active moiety led to false test results

This is a seriously harmful situation. Patients are routinely receiving triple, over three times above, the proper dose of a powerful antipsychotic. Manufacturer-recommendations are triple-dose overmedicating patients every day. If a research subject is tested for the clinical effects of Risperidone during the 15/3.9-rule timeframe, the test results will reflect only a Risperidone triple overdose that is increased and worsened by 46% or more of the previous day's residual Paliperidone. The words "active moiety" are a Marketing Department's linguistic smoke screen that has hidden Johnson & Johnson's multi-billion profit-dollars' toxic overmedication of unsuspecting human beings at the hands of unsuspecting medical providers since 1993. That is indeed a major confound.

The problem of active moiety causing false test results also affects research into the effects of serum concentrations on synapse activity. For example, a 1999 study by Nyberg et al. [19] seemed at first to yield data that was directly pertinent to this paper for calculating the minimum threshold of chemical-Risperidone to activate synapse responses. The study was titled: "Suggested Minimal Effective Dose of Risperidone Based On PET-Measured D2 and 5-HT2A Receptor Occupancy in Schizophrenic Patients" but the test results were false. Blood samples were drawn in the morning before a twice per day medication was ingested. If a 3-hour Risperidone half-life is accurate (see the section of this paper titled "Half-life" above), blood samples were drawn at end of four half-life cycles and only 6.25% remained from the previous twice per day dose. If the samples were drawn one hour later, the results would have been radically different. The listed results were not of chemical-Risperidone but rather of Paliperidone. PET scans were started by the 4-hour mark, but the procedure was 2.5 hours long and ran well beyond the 4-hour mark. Therefore the PET scans measured the effects of Paliperidone, not Risperidone. The study looked hopeful on the surface but did not have the timing that would measure differential-activation. This is an example of the concept of active-moiety confusing Risperidone with Paliperidone and causing inaccurate biological test results. Testing and statistics based on active-moiety fail to take into account the 4-hour duration of Risperidone and the non-applicability of "half-life".

The concept of active moiety led to gynecomastia male breast enlargement

Few people are aware of a 2005 research study that found that Risperidone is not the biochemical culprit behind increased Prolactin levels and Gynecomastia. Rather, Paliperidone is to blame [5]. Additional studies also have confirmed this but to little or no avail. Frankly, there was no avail to be had. In the eyes of the Research Community it was just another fact that didn't solve anything. No one paid much attention.

This research paper is the first to do many things. In addition to those "firsts" that were mentioned earlier, to this author's best knowledge, this is the first paper to solve the Risperidone-dilemma of increased Prolactin and Gynecomastia [21-28].

The solution is quite simple. Gynecomastia is a caused by excessive Prolactin. Excessive Prolactin is caused by Paliperidone activation. Paliperidone is activated by high doses of Risperidone (vis á vis traditional active moiety dose-amounts). This paper presents a method that neutralizes Paliperidone by using low amounts of Risperidone. Differential-activation prevents Paliperidone activation. This prevents Prolactin increases and Gynecomastia.

CONCLUSION

When Bipolar-medication grogginess occurs, it is real and it is not the patient's fault. It usually leads to "poor adherence" and quitting treatment. "Poor adherence" happens by true necessity because a person should discontinue treatments that induce harm. Quitting therapy also happens by true necessity because providers who overmedicate people are inept and patients should leave rather than rely on them. Every incident of side effects reinforces a Bipolar-family's fears and they deride members who "get help." Fearful families are highly unlikely to encourage treatment for America's 2,840,000 people with untreated severe Bipolar Disorders. A study in Korea reported a rapid increase in treatment dropout rates from month-1 (10.9%) to month-3 (24.7%) and it was 50.2% at month-36. Treatment providers told the researchers that the main reasons for quitting treatment were patients' denial of need, lack of efficacy, and patients' poor understanding of treatment effects. The providers were correct about "lack of efficacy" but they wrongly blamed patients' "denial" and "poor understanding of treatment effects."

This paper showed that widely accepted treatments for Bipolar Disorders are actually harmful to patients. Harmful treatments certainly "lack efficacy". Patients who quit harmful treatments are actually showing "good understanding of harmful treatment effects." Their awareness that they are being harmed is awareness that treatment "lacks efficacy." Providers wrongly say patients deny that they need help but patients quit treatment because it does not help. They quit because the treatment harms them. Providers' innate natural ego-defenses cannot see that the providers' are doing harm, so the patients are blamed for having poor insight. The patient-oriented truth is that patients appropriately refuse to continue accepting harmful prescriptions. Providers believe the medications are helpful because that is what they are taught to believe. Because they sincerely believe the medications are helpful, they do not believe patients who say the medications are bad. Providers tell each other, and tell themselves, that these are Bipolar Disorder patients who are crazy so it doesn't matter what they say about the medications. Therefore the widely accepted methods of treatment continue to be used and continue an 82% to 87% rate of failure.

This paper presents a vastly superior treatment for Bipolar Disorders. This author's patients have used this method since 2008. None have quit the treatment or said they want to return to their previous treatments. These patients are benefiting from

a treatment that is very different from all others. It is the most important and valuable advent in Mental Health. The history of Bipolar Disorder treatment is an abysmal 82-87% failure. This paper presents the first successful treatment for Bipolar Disorders.

The challenge of creating a successful method for treating Bipolar Disorders has been met and overcome.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

CONSENT FOR PUBLICATION

Four of this author's Bipolar Disorder patients and two household members signed statements allowing this paper to include and publish some of their treatment information. They were not study-participants. No experiments were conducted.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article and its supplementary information files.

COMPETING INTERESTS

The author declares he has no competing interests.

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AUTHORS' CONTRIBUTIONS

RT was the sole contributing author of this manuscript.

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